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Editorials

Prevention of Malaria

In 1990, the World Health Organization estimated that 2.1 billion people live in malarious areas of the world and that 270 million people develop new malaria infections each year.[1] Although transmission of malaria was interrupted in the United States in the early 1950s, it is still a major concern to the 7 million Americans who visit countries with malaria every year.

See also pp 317, 361, and 383.

Several years ago I was asked to consult on a patient with cerebral malaria. The patient had visited Kenya (East Africa) on safari several weeks earlier and had not taken chemoprophylaxis. Eight days before I saw him he developed fever and headache, and 2 days later he presented to an emergency department with the chief complaint, "I have malaria." The malaria smear was reported as negative (review revealed low parasitemia). The physician prescribed an antipyretic and follow-up in 2 days if his condition did not improve. Three days later the patient returned with bloody diarrhea and intermittent hallucinations and was admitted with a diagnosis of dysentery. The hematology technician noted *Plasmodium falciparum* parasites when examining a thin film for a differential cell count, and oral chloroquine was started. The fact that 35% of his erythrocytes were parasitized was overlooked. When I first saw the patient 3 days later, he was comatose with renal failure, sepsis, pneumonia, and adult respiratory distress syndrome. He never regained normal consciousness and subsequently died. All symptoms and signs were due to malaria and its complications.

Malaria almost certainly would have been *prevented* if the individual had taken appropriate chemoprophylaxis. The development of severe malaria would have been *prevented* if the malaria slide had been reviewed by a pathologist the following day, or if the emergency department physician had insisted on repeat malaria smears every 6 to 12 hours for the next 48 hours and if appropriate oral therapy had been initiated when malaria was detected. Death might have been *prevented* if the admitting physician had recognized severe malaria, placed the patient in an intensive care unit, and initiated appropriate intravenous antimalarial and supportive therapy. Unfortunately, none of these interventions occurred. This is not an isolated event. From 1959 to 1987, 68 US travelers died of malaria in the United States. Seventy-seven percent of these persons did not take chemoprophylaxis, 13% took inappropriate chemoprophylaxis, and 40% of the cases were misdiagnosed.[2]

From the 1940s until the early 1970s, US physicians relied on chloroquine for prevention and treatment of blood-stage malaria infections and on primaquine phosphate to eliminate the slowly developing liver stages of *Plasmodium vivax*. All four human malaria parasites were sensitive to chloroquine and the drug was generally well tolerated. However, beginning in Thailand and Colombia in the late 1950s, chloroquine-resistant *P falciparum* spread throughout the world. In 1980, the problem was primarily confined to South America, Southeast Asia, and Oceania. In 1990, chloroquine resistance has been documented from all malarious areas of the world except for the island of Hispaniola in the Carribean, Central America above Panama, and the Middle East. Most striking has been its rapid march from East to West Africa.

This point is clearly made by Lackritz et al.[3] In 1986 to 1987, the estimated incidence of *P falciparum* malaria was the same in visitors to East Africa who did and did not take chloroquine chemoprophylaxis; chloroquine was ineffective in preventing *P falciparum* infection. In 1985, only 10% of US travelers to West Africa who developed *P falciparum* infection had taken chloroquine chemoprophylaxis. By 1988, the proportion had increased to 48%. This incursion of chloroquine resistance into West Africa in the late 1980s was poignantly illustrated among US Peace Corps volunteers who took chloroquine chemoprophylaxis. In one West African country, Benin, the monthly incidence of *P falciparum* infection in volunteers was essentially nil in 1986, and it was greater than 15% in 1987.[4] Furthermore, Lobel et al[5] now show that the combination of chloroquine and proguanil is not efficacious in Peace Corps volunteers in West Africa. The demise of an almost ideal drug for the prevention and treatment of malaria has provoked an intensive search for new antimalarial drugs.

Lobel et al also report on the use of mefloquine hydrochloride (Lariam), an antimalarial approved for use by the Food and Drug Administration in March 1989. Mefloquine was discovered at the Walter Reed Army Institute of Research

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nearly 20 years ago. Testing indicated that this quinoline methanol, similar in structure to quinine, might be an ideal antimalarial.[1] Like chloroquine, mefloquine is effective against all four human malarias. Although scattered cases of in vitro[2] and in vivo[3] resistance to mefloquine were identified in the early 1980s, and the prevalence of mefloquine resistance has been slowly increasing in Thailand since the widespread introduction of a combination of mefloquine and pyrimethamine-sulfadoxine several years ago, the majority of chloroquine-resistant *P falciparum* parasites have been sensitive to mefloquine. In contrast to chloroquine, which is administered over a 48-hour period, mefloquine can be administered as a single dose because of its long half-life. Thus, its introduction into the United States last year was greeted with enthusiasm by practitioners of travel and tropical medicine. However, because of the prolonged half-life and because toxic effects had been noted at therapeutic levels (World Health Organization, unpublished data, 1989), there was controversy regarding the appropriate interval between prophylactic doses. Based on computer modeling, but not on experimental evidence, it was recommended weekly for 4 weeks, and then every other week.

Lobel et al have identified 17 failures of mefloquine chemoprophylaxis in Peace Corps volunteers taking mefloquine every 2 weeks. In all cases, clinical symptoms first manifested during the second week after drug administration, at a time when the volunteers' mefloquine levels were less than 400 ng/mL. They interpret the findings to indicate that the drug must be given every week and recommendations have been changed accordingly.[11] Also, despite concern over potential toxic effects, the authors point out that no serious adverse reactions occurred in the 264 Peace Corps volunteers in their study and in more than 10 000 European tourists[12] who have taken mefloquine chemoprophylaxis.

Essentially all efforts to prevent malaria have focused on the use of drugs like chloroquine and mefloquine that kill the parasite after it has invaded erythrocytes. There has been little interest in drugs that attack the parasite while it is developing within hepatocytes and before it emerges to infect erythrocytes and cause malaria disease. More than 30 years ago it was shown that administration of 30-mg base of the 8-aminoquinoline, primaquine, on day 1 or 3 after exposure prevented sporozoite-induced malaria.[13] When administered as a phosphate salt, primaquine has a half-life of only 3 to 7 hours and because of its potential toxic effects has not been used the two or three times per week that would be needed for effective chemoprophylaxis. However, more potent 8-aminoquinolines are being developed, and in the future such drugs may be used to prevent malaria.

Malaria prevention is difficult and likely to change during the coming years. No drug can be considered universally efficacious, and although there are currently major efforts to develop malaria vaccines,[14,15] none are in general use. Thus, even when visitors to malarious areas take recommended chemoprophylaxis, they must be aware that they cannot be certain of protection, and they should reduce exposure by using bed netting, insect repellants, and protective clothing. Perhaps even more important, these individuals and their physicians must remember to consider malaria when fever develops in the 1 to 2 years after exposure. When they do not, the outcome can be devastating.

Stephen L. Hoffman, MD, DTMH

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